Complete Summary

GUIDELINE TITLE

Treatment for anemia with erythropoietic agents in patients with non-myeloid hematological malignancies: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Shehata N, Walker I, Meyer R, Haynes AE, Imrie K, Hematology Disease Site Group. Treatment for anemia with erythropoietic agents in patients with non-myeloid hematological malignancies: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2007 Jan 17. 32 p. (Evidence-based series; no. 6-12). [67 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

**** REGULATORY ALERT ****

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- July 31, 2008, Erythropoiesis Stimulating Agents (ESAs): Amgen and the U.S. Food and Drug Administration (FDA) informed healthcare professionals of modifications to certain sections of the Boxed Warnings, Indications and Usage, and Dosage and Administration sections of prescribing information for Erythropoiesis Stimulating Agents (ESAs). The changes clarify the FDA-approved conditions for use of ESAs in patients with cancer and revise directions for dosing to state the hemoglobin level at which treatment with an ESA should be initiated.
- November 8, 2007 and January 3, 2008 Update, Erythropoiesis Stimulating Agents (ESAs): The U.S. Food and Drug Administration (FDA) notified healthcare professionals of revised boxed warnings and other safety-related product labeling changes for erythropoiesis-stimulating agents (ESAs) stating

serious adverse events, such as tumor growth and shortened survival in patients with advanced cancer and chronic kidney failure.

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SCOPE

DISEASE/CONDITION(S)

- Multiple myeloma
- Non-Hodgkin's lymphoma
- Chronic lymphocytic leukemia
- Hodgkin lymphoma

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate if the use of erythropoietic agents affects survival, quality of life, transfusion requirements, correction of anemia, and adverse events in adult patients with non-myeloid hematological malignancies who are at risk for developing anemia during the course, and therapy of their illness

TARGET POPULATION

Adult patients with multiple myeloma, non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and Hodgkin lymphoma who are receiving chemotherapy and meet the following criteria:

- Hemoglobin levels of 100 g/L or less and are likely to require transfusions.

INTERVENTIONS AND PRACTICES CONSIDERED

1. Erythropoietin
2. Darbepoetin alpha

MAJOR OUTCOMES CONSIDERED

- Survival
- Quality of life
- Transfusion requirements
- Correction of anemia
- Adverse events

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A systematic search of the databases was initially conducted in 2000 for erythropoietin and was repeated in 2005 for erythropoietin and darbepoetin alpha, in MEDLINE (1985 to December 2005), CANCERLIT (1985 through October 2005), EMBASE (1985 to December 2005), and the Cochrane Library (2005, Issue 4). The search began from the year 1985, as this was when human erythropoietin was first cloned (30). The search terms included exp lymphoma, lymphoma.ti., lymphoma (MESH), exp multiple myeloma, multiple myeloma.ti., multiple myeloma.mp., and multiple myeloma (MESH). These terms were combined with: exp erythropoietin, erythropoietin.ti., erythropoietin (MESH), exp epogen, epogen.ti., epogen (MESH), exp epo, epo.ti., epo (MESH), exp epoetin, epoetin.ti., epoetin (MESH), exp eprex, eprex.ti., and eprex (MESH) exp darbepoetin, darbepoetin ti. Those terms were combined with the search terms for practice guidelines, meta-analyses, systematic reviews, randomized controlled trials, and controlled clinical trials. The search was then limited to the English language and adults.

The Physician Data Query (PDQ) clinical trials database (http://www.cancer.gov/cancertopics/pdq/cancerdatabase), the United States National Institute of Health Clinical Trials database (http://www.clinicaltrials.gov), and the conference proceedings from the American Society of Clinical Oncology (ASCO) (1996-2005) and the American Society of Hematology (ASH) (1996-2005) were also searched. In addition, reference lists from relevant articles and the

authors' personal files were searched. Ortho-Biotec, the distributor of Eprex® (epoetin alpha), was contacted for additional references and information on ongoing trials.

One other search was conducted, a separate search for patients with chronic lymphocytic leukemia (CLL), as articles in the initial literature search had included a considerable number of patients with chronic lymphocytic leukemia. The same systematic search strategy as per above was conducted to identify trials evaluating erythropoietin/darbepoetin in these patients. The search terms included: exp CLL, CLL.ti., CLL.mp., CLL (MESH), exp chronic lymphocytic leukemia, chronic lymphocytic leukemia.ti., chronic lymphocytic leukemia.mp., and chronic lymphocytic leukemia (MESH).

Study Selection Criteria

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts fulfilling the following criteria:

1. Randomized controlled trials (RCTs) involving the use of either erythropoietin or darbepoetin alpha as an intervention in patients with non-Hodgkin's lymphoma (NHL), Hodgkin lymphoma, multiple myeloma, or CLL.
2. Trials including one of the following primary outcome measures: survival, transfusion requirements, quality of life, correction/improvement of anemia, or adverse events.
3. Systematic reviews, meta-analyses, or evidence-based practice guidelines assessing erythropoietic agents in patients with non-myeloid hematologic malignancies.

Exclusion Criteria

Articles were excluded if:

1. They were non-randomized, phase I, or phase II trials.
2. Hematological patients could not be differentiated from oncology patients.
3. They included patients with acquired immunodeficiency syndrome-associated lymphoma.
4. They included multiple myeloma patients with renal failure requiring hemodialysis.
5. They only included patients having peripheral blood stem cell transplants.
6. They were published in a language other than English.
7. They were letters or editorials.

NUMBER OF SOURCE DOCUMENTS

Twelve randomized controlled trials (RCTs), 3 RCTs in abstract form only, 1 systematic review, 1 systematic review in abstract form, 5 practice guidelines, and 1 pooled analysis of 4 trials were identified.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The parameters considered for pooling were the increment in the level of hemoglobin, the proportion of patients transfused, transfusion requirements, quality of life, survival, and adverse events. The reporting of these parameters was inconsistent among the trials. A hemoglobin increment was reported as a mean hemoglobin increment, mean hemoglobin, median hemoglobin, or mean hemoglobin increment per week. Units of measurement for red cells transfused were mean units, median units, or total units. Seven trials reported on the proportion of patients transfused but used different transfusion triggers and hemoglobin criteria for entry. Many of the trial reports did not contain sufficient data for pooling the outcomes of interest. In addition, a Cochrane review, that was last updated in 2004, included a meta-analysis with subgroup data available for the trials of patients with non-myeloid hematological malignancies. The authors of the Cochrane review obtained updated patient data for the included trials. Due to the variation in reporting, the small amount of data available for pooling in the trial reports, and the availability of a meta-analysis with updated patient data, the authors of this systematic review decided against pooling the aggregate trial data. Due to methodological limitations in quality of life assessments, quality of life results were also not pooled. In addition, none of the trials included survival as a primary outcome.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Assessment of Components Contributing to Recommendations

Quality of Life

To enable an adequate critical appraisal of quality of life indices, the description of quality of life instruments used in the studies and the assessments of those measures are detailed in Appendix I of the original guideline document.

The impact of erythropoietic agents on quality of life is difficult to assess. Six of the seven trials included in this review reported improvement in some quality of life parameter. However, these reports did not follow the proposed guidelines for analyzing, interpreting, and reporting quality of life measures. Recommendations for reporting quality of life include reporting raw scores, reporting the proportion of patients who improve, detailing methods of handling missing data, and defining clinically important differences, and significant limitations in these properties were identified in each report. In particular, missing data can have important implications for the validity of an oncology study, as missing values are likely related to the underlying illness (i.e., patients who drop out or miss appointments are likely to be the sicker patients). Given these limitations, we could not reach definitive conclusions regarding the influence of erythropoietic agents on quality of life in patients with hematologic malignancies. American Society of Clinical Oncology (ASCO) and American Society of Hematology (ASH) reached a similar conclusion in their evidence-based guidelines on the use of erythropoietin in patients with cancer.

Heterogeneity of Response to Erythropoietic Agents

The reviewed studies varied in inclusion criteria, transfusion triggers, dosing regimens, durations of assessment, and the use of co-interventions. Inclusion criteria for hemoglobin requirements ranged from less than 80 g/L to less than 110 g/L. Transfusion thresholds ranged from 70 g/L to 100 g/L. Variation of the transfusion threshold may exaggerate or minimize the effects of either erythropoietin or darbepoetin alpha. The dose of the erythropoietic agent, the increments in the dose during the trial, the chemotherapy regimens, and the timing of the initiation of chemotherapy and the erythropoietic agent also differed among the studies.

The reporting of renal insufficiency was variable. As renal insufficiency would further contribute to anemia and inadequate erythropoietin production, the number of patients included with decreased renal function might affect the results showing the responsiveness of patients to erythropoietic agents. Four studies did not state the creatinine levels of patients entered into their trials. Only one study included patients with a normal range of serum creatinine, and two indicated a creatinine level for inclusion.

The monitoring for iron deficiency and the use of iron supplementation also differed among the studies. Iron indices used to detect iron deficiency are known to inconsistently detect iron deficiency in patients with malignancy. As iron deficiency may occur with erythropoietin or darbepoetin alpha therapy, and may account for a poor response to such therapy, the use or omission of iron supplementation may impact on the degree of the hemoglobin increment. Some authors feel that iron therapy should be initiated for all patients who receive an erythropoietic agent, unless their serum iron or iron saturation is elevated. One study indicated that iron therapy would be initiated when the serum ferritin fell below 100mg/ml. Two studies administered iron to all patients. The remainder of the trials indicated that they would initiate iron depending on the iron indices or did not mention whether iron deficiency would be investigated or left the decision to the discretion of the investigators.

Because of this heterogeneity, and given the conclusions already reached by the Cochrane meta-analysis, we did not perform another meta-analysis.

Predictors of Response

Various parameters have been considered in trying to establish predictors of response to erythropoietin or darbepoetin alpha therapy, including an early change in hemoglobin concentration, an increase in reticulocyte count, the platelet count, the pretreatment endogenous erythropoietin level, and the observed/predicted (O/P) erythropoietin ratio (the O/P ratio is a ratio that was formulated to determine the appropriate erythropoietin response to anemia). The utility of any of the above parameters in the prediction of response to either erythropoietin or darbepoetin alpha has not been established prospectively in trials. Predictors of response to erythropoietic agents for adequate patient selection, therefore, cannot yet be determined.

Adverse Events

Therapy with erythropoietic agents appears to be well tolerated in most patients. Hypertension is a known adverse event associated with erythropoietic agents.

Disease Site Group (DSG) Consensus and Recommendations

The Hematology DSG recognizes that survival, quality of life, and economic benefit are important outcome measures that should influence the decision to adopt new therapies. The importance of transfusion avoidance as an endpoint that should influence practice was debated. The DSG recognized significant limitations to chronic transfusion therapy, notably increasingly limited availability, increasing cost and complexity, and the potential risks of emerging infections. These factors, as well as the recommendations of the Commission of Inquiry on the Blood System in Canada stressing the importance of alternatives to transfusion, influenced the DSG to consider the avoidance of transfusion to be an outcome measure of sufficient importance to guide practice. Although anemia was an outcome measure in many of the identified trials, the members of the Hematology DSG considered it to be an intermediate outcome and only to be of significance if a change in hemoglobin affected survival, transfusion requirements, or quality of life.

With respect to survival, the DSG did not find any evidence to suggest a treatment effect. As indicated above, the DSG also concluded that there is insufficient evidence of erythropoietic agents influencing quality of life to allow for a recommendation that treatment be given to improve this outcome. In contrast, the DSG found the evidence that erythropoietic agents reduce the requirements for transfusion to be sufficiently compelling to recommend therapy for this purpose. The absolute risk reduction in transfusions ranged from 15% to 24%, and the number needed to treat to prevent a transfusion ranged from four to six.

The DSG had difficulty in defining a precise threshold that identifies patients who may be at risk of requiring transfusion. Based on consensus, the threshold hemoglobin value of 100 g/L recommended by American Society of Hematology/American Society of Clinical Oncology (ASH/ASCO) and the Cancer Care Ontario (CCO) Systemic Treatment DSG in their guidelines was endorsed as

a reasonable value. As there are no clear predictors for a response to erythropoietic agents, the DSG felt that this therapy should be offered to patients who fulfill the above criteria.

The Hematology DSG discussed the relative merits of erythropoietin and darbepoetin alpha. Randomized trials of both agents demonstrated a reduction in red cell transfusion requirement. The DSG considered that, while the magnitude of benefit in transfusion requirement appeared to be comparable with both agents, the evidence in support of erythropoietin was more abundant and mature. For this reason, at this time, the DSG recommends that erythropoietin be considered the preferred agent in patients with hematologic malignancies.

In considering dosing for erythropoietic agents, the Hematology DSG acknowledged that the optimum dose has not yet been determined for either erythropoietin or darbepoetin alpha. However, several trials have used erythropoietin at 150 IU/kg three times per week or 40,000 IU weekly, and those doses were considered reasonable. For darbepoetin alpha, there have only been two reports of its use in patients with hematologic cancers, a dose-finding study, and one report using the 2.25 µg/kg once-weekly dosing regimen. In patients with non-hematologic malignancies, a number of dosing regimens have been reported, 2.25 µg/kg weekly, 200 µg flat-dose every two weeks, and 500 µg flat-dose every three weeks for three doses followed by 300 µg every three weeks.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Prior to the submission of this Evidence-based Series report for external review, the report was reviewed and approved by the Program in Evidence-based Care (PEBC) Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues.

Feedback was obtained through a mailed survey of 74 practitioners in Ontario who treat hematological malignancies (hematologists and medical oncologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on July 20, 2006. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed

again). The Hematology Disease Site Group (DSG) reviewed the results of the survey.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Erythropoietic agents are recommended as a treatment option for patients with non-myeloid hematological malignancies who are receiving chemotherapy and who require or are likely to require red blood cell transfusions.
- Erythropoietin and darbepoetin alpha are both acceptable options for patients in whom treatment with erythropoietic agents is planned.
- Erythropoietic agents are not recommended when rapid correction of hemoglobin is required.
- There is insufficient evidence to draw conclusions regarding the effects of erythropoietic agents on quality of life or survival.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials (RCTs), systematic reviews, practice guidelines, and 1 pooled analysis of 4 trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Six studies assessed quality of life, using validated instruments. There were methodological problems with five of those trials that limit any inference about the quality of life with erythropoietic agents. The sixth trial reported no statistically significant difference in quality of life scores for patients who received erythropoietin compared to placebo.
- Five of 15 trials found a statistically significant improvement in transfusion requirements. The proportion of patients transfused was dependant on transfusion triggers; the reduction in the proportion transfused ranged between 15% and 24%, and the number needed to treat to prevent a transfusion ranged from four to six.

POTENTIAL HARMS

Trials of Erythropoietin

In all five trials, there were no statistically significant differences in the frequency of adverse events and mortality between treatment and control groups. Erythropoietin therapy may have contributed to two deaths (in an elderly patient who had a stroke and a patient who had a pulmonary embolus). More patients in the epoetin beta arms, in the trial by Osterborg et al, died from infections/septicemia but none of the deaths was attributed to the treatment regimens. Two patients had an increase in the level of monoclonal protein coincident with an increase in the epoetin alpha dose in the trial by Silvestris et al.

Trials of Darbepoetin Alpha

The dose finding trial by Hedenus et al reported that the most common adverse events were nausea, fatigue, fever, peripheral edema, abdominal pain, back pain, vomiting, constipation, diarrhea, dyspnea, and upper respiratory infection. The percentages of patients who experienced an adverse event were similar for peripheral edema and diarrhea. The remaining adverse events occurred in more patients for the placebo group compared to the darbepoetin alpha group. The most common adverse events in the more recent trial reported by Hedenus et al were fatigue, fever, nausea, diarrhea, vomiting, dyspnea, and constipation, with the percentage of patients who experienced an adverse event being similar for both the darbepoetin alpha group and the placebo group.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- As evidence supporting the role of erythropoietin is more abundant and mature than that in support of darbepoetin alpha in patients with lymphoma or myeloma, at this time, the Disease Site Group (DSG) recommends erythropoietin as the preferred agent.
- As there are no clear predictors for response to erythropoietic agents, it was felt that this therapy should be offered to all patients who fulfill the above criteria.
- Dose modifications according to the product monograph should be adhered to in order to prevent thrombotic events.
- Acceptable dosing regimens for erythropoietin are 150 IU/kg subcutaneously three times per week or 40,000 U weekly, although the optimal dosing schedule has not been determined. Approved dosing regimens may be found in the product monograph.
- Common dosing strategies used for darbepoetin alpha are 2.25 µg/kg weekly, a flat dose of 200 µg every two weeks, or a flat dose of 500 µg every three weeks for three doses followed by 300 µg every three weeks. Insufficient comparative evidence currently exists to determine the optimal dosing strategy. However, approved dosing regimens may be found in the product monograph.
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Shehata N, Walker I, Meyer R, Haynes AE, Imrie K, Hematology Disease Site Group. Treatment for anemia with erythropoietic agents in patients with non-myeloid hematological malignancies: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2007 Jan 17. 32 p. (Evidence-based series; no. 6-12). [67 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2007 Jan 17

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Hematology Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Hematology Disease Site Group (DSG) were asked to disclose potential conflict of interest information. Dr. N. Shehata received an honorarium from Ortho-Biotec for a presentation on the use of erythropoietin for patients with multiple myeloma and non-Hodgkin's lymphoma (NHL) in 1999. No other potential conflicts were declared.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Treatment for anemia with erythropoietic agents in patients with non-myeloid hematological malignancies: a clinical practice guideline. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2007 Jan 17. Various p. (Practice guideline; no. 6-12). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on March 19 2007. The information was verified by the guideline developer on April 12, 2007. This summary was updated by ECRI Institute on July 9, 2007, following the FDA advisory on erythropoiesis stimulating agents. This summary was updated by ECRI Institute on March 21, 2008 following the FDA advisory on Erythropoiesis Stimulating Agents. This summary was updated by ECRI Institute on August 15, 2008 following the U.S. Food and Drug Administration advisory on Erythropoiesis Stimulating Agents (ESAs).

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